Purpose and aim

The overall aims of this proposal are to improve, optimise and equalise maternal and delivery care during pregnancy in order to limit adverse consequences for both the mother and infant, by:

- Validating the Fetal Medicine Foundation[1] prediction model for detection of *preterm (< 37 gestational weeks)* preeclampsia in a Swedish population.
- Creating a Swedish prediction model with population-specific riskfactors, optimized for the Swedish health care system for identifying high-risk women for *preterm* preeclampsia in order to be able to start aspirin prophylaxis, which has been proven to reduce the risk of developing *preterm* preeclampsia by 50%.[1,2]
- Creating a prediction model for identifying high-risk women for *overall* preeclampsia during pregnancy and birth of a small for gestational age infant in order to plan individualized surveillance for early detection, which has been proven beneficial for both the mother and infant.[3,4,5,6]
- Creating a national biobank with blood samples and individual clinical registry data including pregnancy outcomes enabling future research on prevention and early detection for various adverse pregnancy outcomes.

Survey of the field

Swedish risk assessment for preeclampsia in early pregnancy is still obtained by maternal history and characteristics, which only detects about 30% of women that will develop preeclampsia. Risk factors are evaluated individually without being incorporated into a combined model that would allow multivariable analysis. This approach has been proven to be poor due to low specificity and sensitivity.[7] Lately a more complex prediction model has been developed by the Fetal Medicine Foundation, using multivariable analysis and including serum biomarkers and physiological measurements reflecting maternal adaption to pregnancy.[8] Intervention with aspirin given to identified high-risk pregnancies according this model has has been shown to decrease the incidence of *preterm (< 37 gestational weeks)* preeclampsia (OR: 0.38; 95% CI 0.20-0.74), compared to placebo.[1] Detection rates and cut-off values have been shown to vary between populations,[9,10,11] depending on differences in population characteristics and incidence of disease, overfitting of the original model and differences in healthcare systems. Therefore, the model needs to be validated in Sweden. Further, the Fetal Medicine Foundation-model includes expensive covariates such as several biochemical markers and uterine artery Doppler.[8,12] There is a need to create, validate and implement a cost-effective prediction model for first trimester screening for preeclampsia in a Swedish population, with the purpose to select who might benefit from aspirin prophylaxis to prevent *preterm* preeclampsia.

Early detection of preeclampsia remains one of the major focuses of maternal health care and is emphasised by the WHO, since it has proven to be beneficial for both the mother and unborn child.[3,4] Small-for-gestational-age fetuses not identified before delivery have an increased risk of adverse perinatal outcomes, compared to those identified during pregnancy.[5,6] Identification of high-risk pregnancies is therefore important in early pregnancy to plan for prophylactic interventions, to optimize surveillance and to plan deliveries. Today most Swedish women attend the same maternal health care program with increasing number of visits in the end of pregnancy. By risk identification in early pregnancy we can individualize

maternal health care and target women at high risk early in pregnancy. High-risk pregnancies can be referred to specialized health care and normal pregnancies followed at the basic maternal health care.

The Swedish registry data is unique and combining it with a biobank containing blood samples from the first trimester could improve maternal healthcare and in the long run reduce adverse outcomes for Swedish women.[13] A national first trimester pregnancy biobank would facilitate future research on prevention and prediction of pregnancy complications.

Study design
A prospective national multi-center cohort study for prediction of preeclampsia will be conducted. The study is supported by the SNAKS (Svenskt nätverk för Nationella Kliniska Studier inom Obstetrik och Gynekologi) consortium, meaning that the study has a network to all obstetrical units in Sweden.
Women will be approached with information about the study at the time of the first antenatal visit at the maternal health care. We will recruit pregnant women attending a first trimester scan in pregnancy at 11-14 weeks' gestation. Today 75% of OB/Gyn departments in Sweden offer a first trimester scan (CUB and/or dating) where about 75-90% of the women attend.

Patient selection
Inclusion criteria: Women with a Swedish personal identity number, who adhere to maternal care program before the end of the first trimester and have a planned first trimester scan are elegible for the study. Women will be included after receiving written information and given informed concent.
Exclusion criteria:
Maternal age <18 years or language-barrier despite interpreter and written information.

Variables and measures
A number of maternal characteristics such as existing chronic disease before pregnancy, family history, socioeconomic factors, physical characteristics and characteristics of previous pregnancies will be used and kept as the highest order possible regarding continuous, nominal, binary or ordinal varibles. Most clinical variables will be collected from the first antenatal visit, obtained from the Swedish Pregnancy Register.[14] The variables not available in the Pregnancy Register will be collected at the first trimester scan visit and registered in the clinically used CUB (combined ultrasound and biochemistry risk assessment)-module, currently used for calculation of risk of aneuploidy in the end of the first trimester. Examples of extra variables are ongoing aspirin treatment (including dose) and preeclampsia in former pregnancies. The CUB-module will be modified for the study both in order to include the extra variables (that will appear after the examiner has ticked the box that informed consent is obtained) and to enable to switch off the aneuploidy-testing if needed (allowing the module to only collect data for the present study). The CUB-module and the Pregnancy register both use MedSciNet as IT-platform,[15] which enables merging of data.

In addition, a standardized blood pressure (mean arterial pressure) and uterine pulsatile index estimated by Doppler ultrasound as continuous variables collected at the first trimester scan visit will be added to the CUB-module. Further, a blood sample will be collected enabling to analyse Placental Growth Factor levels. At all participating centers, the blood samples for PlGF analyses might be frozen locally at the laboratory for later joint analysis after inclusions are finished. Data from the Pregnancy register and the CUB-module will all be considered as predictors for outcome and models will be built with different combinations of 5-15 variables.

Outcome variables will be collected from the Swedish Pregnancy registry and will consist of delivery and diagnosis of preeclampsia by ICD codes or small for gestational age defined as

birthweight ≤ - 2 SD according to the Swedish reference curve.[16] The outcome variables have the potential to be treated both as continuous or binary. As binary they will be divided into *early onset* (diagnosis of preeclampsia and delivery <34 weeks), *preterm* (diagnosis and delivery <37 weeks) and *term* (diagnosis and delivery >37 weeks). From the national registers, longterm outcome for mother and child will also be collected for later analyses of longterm outcome such as cardiovascular disease.

Estimated sample size, analysis plan, time line

The prevalence of *preterm* preeclampsia (main outcome) is ~0.7% and we want to be able to include up to 15 covariates/interactions in the final model. Further, we plan to validate the prediction model within the cohort. The assumption of 15 events per estimated parameter in the model leads to a number of births needed to create the model of ~32 000 (100*15*15/0.7). Assuming that we need 100 *preterm* preeclampsia in the validation population, an additional ~14 250 (100*100/0.7) births will be needed, leading to a sample size of 46 250 births for both creation and validation of the model. No formal sample size calculation using usual power considerations can be performed due to the fact that we do not know which predictors that will be included in the final model.

The modelling of *preterm* preeclampsia, *overall* preeclampsia and small for gestational age infant will be made using multiple logistic regression in order to find the best prediction models. All possible covariates/predictors will first be analysed univariably as the only predictor in the model but the main focus will be the multivariable modelling. Depending on the distribution of the variable and its correlation to the outcome, transformation or categorisation might be necessary. Non-linear effects and interaction effects of the covariates/predictors will also be evaluated for the final multivariable model. We will calculate population-based multiple of the median (MoM) reference values for mean arterial pressure and serum-Placental Growth Factor. We will consider ongoing treatment with aspirin in the analyses.

The number of annual births in Sweden is 120,000. At the clinics of the steering committee combined, there are ~34,000 annual pregnancies with a first trimester ultrasound performed annually. Assuming that 2/3 of these pregnancies participate, the inclusion will be accomplished within two years. However, we are planning for additional Swedish clinics to participate, with an estimation of a 1.5 year-recruiting period. The third year of the study will be dedicated to analysis and preparation for implementation of the new Swedish first trimester risk module.

Biobank of Pregnant Women

At centers with biobank possibilities, additional serum, plasma and buffy-coat samples will be collected at the same time as the serum samle for analyse of Placental Growth Factor. The samples for the biobank will be stored for future research related to prediction, diagnosis and prevention of pregnancy complications. Each new project utilizing the biobank requires ethical approval but not informed consent. By merging the participants in the Biobank with the Pregnancy Register, we will create a unique population-based Research Database with individual biological samples, medical, reproductive and social background from early pregnancy and subsequent pregnancy, delivery and infant outcomes.

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